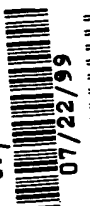


1c542 U.S. PTO
09/359920



07/22/99

424	94.5	Subclass
Class	Issue Classification	

U.S. UTILITY PATENT APPLICATION

DB 2 O.I.P.E.	PATENT DATE
SCANNED <i>Law</i> Q.A. <i>RG</i>	

SECTOR	CLASS 424	SUBCLASS 94.5	ART UNIT	EXAMINER <i>N...</i>
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PREPARED AND APPROVED FOR ISSUE

ISSUING CLASSIFICATION

ORIGINAL		CROSS REFERENCE(S)					
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
424	94.5	424	59	94.6	94.63	401	
INTERNATIONAL CLASSIFICATION		435	16	177	193	196	
A61K	38/00	514	2				
A61K	38/48	530	402	812			
A61K	38/00						
C12N	11/02						
C07K	17/02						

☐ Continued on Issue Slip Inside File Jacket

☐ TERMINAL DISCLAIMER

☐ a) The term of this pat subsequent to _____ has been disclaimed.

☐ b) The term of this pat not extend beyond the exp of U.S Patent. No. _____

☐ c) The terminal _____ this patent have been discl

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DRAWINGS			CLAIMS ALLOWED			
Sheets Drwg. 2	Figs. Drwg. 3	Print Fig. <i>Have</i>	Total Claims 41	Print Claim for O.G. 1		
<p>_____ (Assistant Examiner) (Date)</p> <p><i>DAVID M. NAFF</i> PRIMARY EXAMINER ART UNIT 1851 (Primary Examiner)</p> <p>_____ (Legal Instruments Examiner) (Date)</p>			<p>NOTICE OF ALLOWANCE MAILED</p> <p>ISSUE FEE</p> <table border="1"> <tr> <td>Amount Due</td> <td>Date Paid</td> </tr> </table> <p>ISSUE BATCH NUMBER</p>		Amount Due	Date Paid
Amount Due	Date Paid					

S.S.N. 09/359,920

- 3 -

¹⁹
~~87.~~ (New) The kit of claim ~~77~~, further comprising calcium housed by said package, except that said calcium is not in said second container.

^{LD8}
88. (New) A kit comprising
a package housing:
a first container containing the composition of claim 65, and
a second container containing transglutaminase.

89. (New) The kit of claim 88, further comprising
a third container housed by said package, the third container containing a linking molecule that is
a substrate of transglutaminase and that is covalently attached to the composition contained in the first
container if in the presence of transglutaminase.

³⁸
~~90.~~ (New) The kit of claim ~~88~~, further comprising calcium housed by said package, except that
said calcium is not in said second container.

³¹
~~91.~~ (New) A kit comprising
a package housing:
a first container containing the composition of claim 77, and
a second container containing transglutaminase.

^{20 D10}
92. (New) The kit of claim 91, further comprising
a third container housed by said package, the third container containing a linking molecule that is
a substrate of transglutaminase and that is covalently attached to the composition contained in the first
container if in the presence of transglutaminase.

²²
~~93.~~ (New) The kit of claim ~~91~~, further comprising calcium housed by said package, except that
said calcium is not in said second container.

^{Sub. C11}
94. (New) A kit comprising
a package housing:
a first container containing the composition of claim 67, and
a second container containing transglutaminase.

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- 4 -

95. (New) The kit of claim 94, further comprising
a third container housed by said package, the third container containing a linking molecule that is
a substrate of transglutaminase and that is covalently attached to the composition contained in the first
container if in the presence of transglutaminase.

41 39
96. (New) The kit of claim 94, further comprising calcium housed by said package, except that
said calcium is not in said second container.


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97. (New) A kit comprising
a package housing:
a first container containing the composition of claim 85, and
a second container containing transglutaminase.

98. (New) The kit of claim 97, further comprising
a third container housed by said package, the third container containing a linking molecule that is
a substrate of transglutaminase and that is covalently attached to the composition contained in the first
container if in the presence of transglutaminase.

REMARKS

Applicants have previously paid for 32 total claims and 7 independent claims. There are 32 total
claims and 2 independent claims currently pending. No fee is considered due, however should the
Examiner determine that an additional fee is necessary, he is respectfully requested to charge the
appropriate fee to the account of the undersigned, Deposit Account No. 23/2825.

Respectfully submitted,


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(617) 720-3500

Docket No. H0535/7009 (ERG/MAT)
Date: September 18, 2000
xNDDx

Please re-write the claims as follows:

55. (Amended) A composition of matter comprising:
a conjugate of a nonextracellular matrix protein, nonlabeling agent and a carboxamide-carrying linking molecule,

wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an enzyme, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellent and a component of a high affinity noncovalent coupling pair;

wherein the linking molecule is not native to the agent, and

wherein the linking molecule comprises at least two contiguous linked glutamines, and is a substrate of transglutaminase.

56. (Amended) The composition of claim 55, wherein the linking molecule comprises a polymer of amino acids containing at least 20% glutamines.

66. (Amended) A composition of matter comprising:
a conjugate of a nonextracellular matrix protein, nonlabeling agent and a polymer,
wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an enzyme, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, an insect repellent and a component of a high affinity noncovalent coupling pair, and

wherein the polymer comprises at least 3 contiguous lysines attached to one another by peptide bonds, and is a substrate of transglutaminase.

67. (Amended) The composition of claim 66, wherein the polymer comprises amino acids, and wherein at least 20% of the amino acids are lysines.

57. (Amended) The composition of claim 55, wherein the component of a high affinity noncovalent binding pair is selected from the group consisting of a ligand of a ligand-receptor complex, and a receptor of a ligand-receptor complex.

78. (Amended) The composition of claim 55, wherein the agent is selected from the group consisting of a cholinesterase and a phosphodiesterase.

79. (Amended) The composition of claim ~~55~~¹, wherein the agent is conjugated to the linking molecule by a bond that is hydrolyzable under physiological conditions.

80. (Amended) The composition of claim ~~55~~¹, wherein the agent is a pharmaceutical agent and the agent is conjugated to the linking molecule by a bond that is hydrolyzable under physiological conditions.

82. (Amended) The composition of claim ~~55~~¹, wherein the agent is not itself a substrate of transglutaminase.

83. (Amended) The composition of claim ~~56~~²⁵, wherein the agent is conjugated to the linking molecule by a bond that is hydrolyzable under physiological conditions.

84. (Amended) The composition of claim ~~56~~²⁵, wherein the agent is a nonprotein.

85. (Amended) The composition of claim ~~66~~¹, wherein the agent is not itself a substrate of transglutaminase.

91. (Amended) A kit comprising
a package housing:
a first container containing the composition of claim 81, and
a second container containing transglutaminase.

94. (Amended) A kit comprising
a package housing:
a first container containing the composition of claim ~~84~~²⁸, and
a second container containing transglutaminase.

97. (Amended) A kit comprising
a package housing:
a first container containing the composition of claim ~~102~~¹¹, and
a second container containing transglutaminase.

Please add new claims 99-112 as follows:

99. (New) The composition of claim ~~55~~¹, wherein the agent is an enzyme.

100. (New) The composition of claim ~~56~~²⁵, wherein the agent is an enzyme.

³⁰
101. (New) The composition of claim ²⁹100, wherein the enzyme is selected from the group consisting of a cholinesterase and a phosphodiesterase.

³¹
102. (New) The composition of claim 55, wherein the conjugate is in or on a microparticle.

³²
103. (New) The composition of claim 66, wherein the conjugate is in or on a microparticle.

¹²
104. (New) The composition of claim ¹55, wherein the linking molecule comprises at least three contiguous linked glutamines.

¹³
105. (New) The composition of claim ¹55, wherein the linking molecule comprises at least four contiguous linked glutamines.

¹⁴
106. (New) The composition of claim ¹55, wherein the linking molecule comprises at least five contiguous linked glutamines.

¹⁵
107. (New) The composition of claim ¹55, wherein the linking molecule comprises a polymer of amino acids containing at least 30% glutamines.

¹⁶
108. (New) The composition of claim ¹55, wherein the linking molecule comprises a polymer of amino acids containing at least 40% glutamines.

³²
109. (New) The composition of claim ²⁵60, wherein the polymer comprises at least 4 contiguous lysines attached to one another by peptide bonds.

³³
110. (New) The composition of claim ²⁵60, wherein the polymer comprises at least 5 contiguous lysines attached to one another by peptide bonds.

⁷
111. (New) The composition of claim 66, wherein the polymer comprises amino acids, and wherein at least 30% of the amino acids are lysines.

⁸
112. (New) The composition of claim 66, wherein the polymer comprises amino acids, and wherein at least 40% of the amino acids are lysines.

88 Remarks

priority to U.S. provisional patent application serial no. 60/071,908, filed January 20, 1998,
titled "Transglutaminase Linkage of Agents to Tissue" which is now abandoned. This entire reference
is incorporated herein.

#160
B
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#2

In the Claims

Please delete claims 76, 82 and 85.

A marked-up version of the entire claim set is appended herewith as Appendix A. Please re-write
the entire pending claim set as follows:

1 55. (Twice Amended) A composition of matter comprising:
a conjugate of a nonextracellular matrix protein, nonlabeling agent and a carboxamide-carrying
linking molecule,

wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an
enzyme, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, a
bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory agent, an anti-
nerve gas agent, a film forming agent, a vitamin, an insect repellent and a component of a high affinity
noncovalent coupling pair,

wherein the agent is not itself a substrate of transglutaminase,

wherein the agent, free of conjugation to the linking molecule, does not contain the linking
molecule, and

wherein the linking molecule comprises at least two contiguous linked glutamines, and is a
substrate of transglutaminase.

57. (Once Amended) The composition of claim 55, wherein the linking molecule comprises a
polymer of amino acids containing at least 20% glutamines.

25 56. (Twice Amended) A composition of matter comprising:

a conjugate of a nonextracellular matrix protein, nonlabeling agent and a polymer,

wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an
enzyme, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory
agent, an anti-nerve gas agent, a film forming agent, a vitamin, a coloring agent, a pharmaceutical agent, a
member of a ligand/receptor pair, a tissue sealant, an insect repellent and a component of a high affinity
noncovalent coupling pair,

wherein the agent is not itself a substrate of transglutaminase, and

wherein the polymer comprises at least 3 contiguous lysines attached to one another by peptide bonds, and is a substrate of transglutaminase.

²⁶
67. (Twice Amended) The composition of claim ²⁵66, wherein the polymer is a polymer of amino acids, wherein at least 20% of the amino acids are lysines.

¹⁷
D4 71. (Twice Amended) A kit comprising
a package housing:
a first container containing the composition of claim ¹55 and
a second container containing transglutaminase.

³
D5 74. (Once Amended) The composition of claim ¹55, wherein the linking molecule comprises at least 5 linked units, each unit being a carboxamide-bearing substrate for transglutaminase.

⁴
75. (Once Amended) The composition of claim ¹55, wherein the linking molecule is 4 or more contiguous glutamines attached directly to one another by peptide bonds.

77. (Once Amended) The composition of claim 55, wherein the component of a high affinity noncovalent binding pair is selected from the group consisting of a ligand of a ligand-receptor complex, and a receptor of a ligand-receptor complex.

78. (Once Amended) The composition of claim 55, wherein the agent is selected from the group consisting of a cholinesterase and a phosphodiesterase.

79. (Once Amended) The composition of claim 55, wherein the agent is conjugated to the linking molecule by a bond that is hydrolyzable under physiological conditions.

80. (Once Amended) The composition of claim 55, wherein the agent is a pharmaceutical agent and the agent is conjugated to the linking molecule by a bond that is hydrolyzable under physiological conditions.

⁹
D6 81. (Once Amended) The composition of claim ¹55, wherein the agent is a nonprotein.

83. (Once Amended) The composition of claim 66, wherein the agent is conjugated to the linking molecule by a bond that is hydrolyzable under physiological conditions.

84. (Once Amended) The composition of claim 66, wherein the agent is a nonprotein.

7
18
85. (Once Amended) The kit of claim ~~71~~¹⁷, further comprising a third container housed by said package, the third container containing a linking molecule that is a substrate of transglutaminase and that is capable of covalently attaching to the composition contained in the first container in the presence of transglutaminase when the composition and the linking molecule are removed from the containers and contacted with each other.

87. The kit of claim 71, further comprising calcium housed by said package, except that said calcium is not in said second container.

36
88. (Once Amended) A kit comprising a package housing:
a first container containing the composition of claim ~~66~~²⁵, and
a second container containing transglutaminase.

37
89. (Once Amended) The kit of claim ~~88~~³⁶, further comprising a third container housed by said package, the third container containing a linking molecule that is a substrate of transglutaminase and that is capable of covalently attaching to the composition contained in the first container in the presence of transglutaminase when the composition and the linking molecule are removed from the containers and contacted with each other.

90. The kit of claim 88, further comprising calcium housed by said package, except that said calcium is not in said second container.

20
91. (Once Amended) A kit comprising a package housing:
a first container containing the composition of claim ~~81~~⁹, and
a second container containing transglutaminase.

92. (Once Amended) The kit of claim ~~91~~³⁶, further comprising a third container housed by said package, the third container containing a linking molecule that is a substrate of transglutaminase and that is capable of covalently attaching to the composition contained in the first container in the presence of transglutaminase when the composition and the linking molecule are removed from the containers and contacted with each other.

93. The kit of claim 91, further comprising calcium housed by said package, except that said calcium is not in said second container.

94. (Once Amended) A kit comprising a package housing:
a first container containing the composition of claim 84, and
a second container containing transglutaminase.

95. (Once Amended) The kit of claim ~~94~~³⁹, further comprising a third container housed by said package, the third container containing a linking molecule that is a substrate of transglutaminase and that is capable of covalently attaching to the composition contained in the first container in the presence of transglutaminase when the composition and the linking molecule are removed from the containers and contacted with each other.

96. The kit of claim 94, further comprising calcium housed by said package, except that said calcium is not in said second container.

97. (Once Amended) A kit comprising a package housing:
a first container containing the composition of claim 102, and
a second container containing transglutaminase.

98. (Once Amended) The kit of claim ~~97~~³³, further comprising a third container housed by said package, the third container containing a linking molecule that is a substrate of transglutaminase and that is capable of covalently attaching to the composition contained in the first container in the presence of transglutaminase when the composition and the linking molecule are removed from the containers and contacted with each other.

99. The composition of claim 55, wherein the agent is an enzyme.

100. The composition of claim 66, wherein the agent is an enzyme.

101. The composition of claim 100, wherein the enzyme is selected from the group consisting of a cholinesterase and a phosphodiesterase.

⁴¹
~~102.~~ (Once Amended) The composition of claim ~~55~~, wherein the agent is in a microparticle.

³¹
~~103.~~ (Once Amended) The composition of claim ~~56~~, wherein the agent is in a microparticle.

104. The composition of claim 55, wherein the linking molecule comprises at least three contiguous linked glutamines.

105. The composition of claim 55, wherein the linking molecule comprises at least four contiguous linked glutamines.

106. The composition of claim 55, wherein the linking molecule comprises at least five contiguous linked glutamines.

107. The composition of claim 55, wherein the linking molecule comprises a polymer of amino acids containing at least 30% glutamines.

108. The composition of claim 55, wherein the linking molecule comprises a polymer of amino acids containing at least 40% glutamines.

109. The composition of claim 66, wherein the polymer comprises at least 4 contiguous lysines attached to one another by peptide bonds.

110. The composition of claim 66, wherein the polymer comprises at least 5 contiguous lysines attached to one another by peptide bonds.

¹⁴
~~111.~~ (Once Amended) The composition of claim ~~66~~, wherein the polymer is a polymer of amino acids, wherein at least 30% of the amino acids are lysines.

35
112. (Once Amended) The composition of claim 66, wherein the polymer is a polymer of amino acids, wherein at least 40% of the amino acids are lysines. 25

Remarks

The priority claim in the specification has been amended in order to reflect that the parent application, to which priority was previously claimed, itself claimed priority to a U.S. provisional patent application. The priority claim for U.S. patent application serial no. 09/234,358 was of record in that case. Accordingly, no new matter has been added.

Claims 76, 82 and 85 have been deleted. The subject matter of claims 82 and 85 have been introduced into independent claims 55 and 66, respectively.

Claims 55 and 66 have been amended, in part, to include the limitation that the agent is not itself a substrate of transglutaminase. Support for this amendment can be found in previously pending (and now cancelled) claims 82 and 85.

Claims 55 has been further amended, in part, to clarify the meaning of "the linking molecule is not native to the agent". As suggested by the Examiner, the claim has been amended to recite the limitation that "the agent, free of conjugation to the linking molecule, does not contain the linking molecule". This is not a narrowing amendment.

Claims 67, 111 and 112 have been amended to clarify their meaning at the Examiner's suggestion. These are not narrowing amendments.

Claims 71, 74, 75, 81 and 88 have been amended in order to correct claim dependency.

Claims 86, 89, 92, 95 and 98 have been amended to clarify their meaning at the Examiner's suggestion. These are not narrowing amendments.

Claims 102 and 103 have been amended to reflect that the agent is in the microparticle. Support for these amendments can be found on page 8, line 17, and page 14, line 23.

No new matter has been added.

Claims 55, 57, 66, 67, 71 and 74, 75, 77-112 are currently pending.

Applicants reserve the right to pursue the full breadth of the subject matter of originally filed claims 53 and 65 in a continuing application.

The Claimed Invention

The claimed invention relates, in part, to compositions comprising conjugates of active agents and linking molecules, that can be applied to a body tissue using transglutaminase. The active agents are nonextracellular matrix protein, nonlabeling agents and can include chemical agents such as